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Title:
ANGIOGENIC CHANGES IN A NEW MOUSE MODEL FOR HEPATOCELLULAR CARCINOMA ASSESSED WITH STATE-OF-THE-ART IMAGING TECHNOLOGY

Introduction:
An efficient and representative mouse model is the corner stone of a successful experiment. The growing incidence of hepatocellular carcinoma (HCC) in the Western countries has led to an expanding interest of scientific research in this field. Therefore, there is a vast need of experimental models that mimic the natural pathogenesis of HCC in a short time period. Furthermore, the validation of an efficient imaging technique could contribute to the early detection of HCC in patients.

Aim:
The goal of our study was (1) to develop an efficient mouse model for hepatocellular carcinoma research, (2) to assess time-dependent angiogenic changes and (3) to investigate tumour growth and neo-vascularisation using state-of-the-art imaging techniques.

Methods:
5-week-old male mice received weekly intraperitoneal injections with N-nitrosodiethylamine (DEN) (35 mg/kg bodyweight) and samples were taken at several time points. Histology, ELISA and immunohistochemical stainings were used to identify the HCC-lesions and to quantify angiogenic factors VEGF and PlGF. HCC livers (25W) were perfused with Batson's n°17 solution to produce vascular casts (arterial and venous). A state-of-the-art multimodal microPET/CT was used for in vivo detection of HCC-lesions with [18F]-fluoromethylcholine ([18F]FMCH) and for 3D-reconstruction of the vascular casts.

Results:
After 16W of DEN-injections a mild fibrosis (F1-F2) and dysplastic lesions appear, resulting in a pre-malignant environment. An increase of angiogenic factors VEGF and PlGF takes place, but not explicit enough to induce an increase in endothelial cells, which were upregulated after 20W. After 25W of DEN-injections, the dysplastic lesions have progressed to vascularised exophytic tumours which are macroscopically visible and give rise to a further increase in angiogenic factors, leading to the formation of new blood vessels. HCC-lesions were characterised by an increased uptake of [18F]FMCH, allowing visualisation of these hotspots (>3mm) with microPET/CT. The vascular casts of HCC-livers clearly revealed the chaotic pattern and hierarchically disorganisation of tumour induced blood vessels. Arteries formed a circumferential mantle around the hepatic tumours, while the central tumour regions showed a lower arterial density.

Conclusion:
While most DEN-induced models take at least one year to develop tumours, weekly injections with DEN give rise to tumour occurrence after 25W. The well vascularised orthotopic tumours are a representative model for HCC and can serve as an excellent platform for the development of new therapeutic targets. Furthermore, [18F]FMCH PET imaging may be clinically relevant for the visualization of HCC-lesions.

(Orale presentatie)